UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: March 21, 2013

SUBJECT: Penthiopyrad: Summary of Hazard and Science Policy Council (HASPOC) Meeting of March 14, 2013: Recommendation on the Requirement of a Subchronic Inhalation Study.

PC Code: 090112
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056611
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

FROM: Julie Van Alstine, MPH Julie VanAlstine
Executive Secretary, HASPOC
Health Effects Division (HED; 7509P)

THROUGH: Jess Rowland, Co-Chair
Anna Lowit, Ph.D., Co-Chair
HASPOC
HED (7509P)

TO: Jaime D'Agostino, Toxicologist
Dennis McNeilly, Risk Assessor
Christina Swartz, Chief
Risk Assessment Branch II

And

Matthew Crowley, Occupational Exposure and Risk Assessor
Chemistry and Exposure Branch
HED (7509P)

MEETING ATTENDEES

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jess Rowland, John Kough, Jonathan Chen, Michael Metzger, Ray Kent

Presenters: Jaime D'Agostino

Other Attendees: Angela Howard, Christina Swartz, Dennis McNeilly, Elizabeth Holman, Joey Bever, Margarita Collantes, Matthew Crowley, Monique Perron, Kristin Rury, Julie Van Alstine

I. PURPOSE OF MEETING

A subchronic inhalation study is not available for the fungicide penthiopyrad. Based on current policies, a subchronic inhalation toxicity study is required due to the potential for repeated inhalation exposure. The Hazard and Science Policy Council (HASPOC) met on March 14, 2013 to discuss the need for a subchronic inhalation toxicity study to support the proposed uses of penthiopyrad.

II. SUMMARY OF USE PROFILE & CURRENT RISK ASSESSMENT

Penthiopyrad is a broad-spectrum carboxamide fungicide currently registered for control of foliar and soil-borne plant diseases. Penthiopyrad shows its fungicidal activity by impairing respiration through inhibition of succinate dehydrogenase. Penthiopyrad is currently registered for use on numerous agricultural field crops, residential and recreational area turfgrass, and landscape trees and ornamentals. Risk Assessment Branch II (RAB II) is currently evaluating new proposed seed treatment uses for corn, canola, sugar beet, soybean, and potato seed pieces.

The end use products may be applied through a variety of application methods including: aerial, chemigation, ground, airblast, backpack, hand held (low pressure, high pressure, and hand gun), and hose-end sprayer equipment. The uses on turfgrass and ornamentals result in the potential for both residential and occupational exposures. In addition, because of the agricultural uses, applicators might be exposed while handling the pesticide prior to application, mixing/loading the pesticide, and during application. Also, there is a potential for post-application exposure for workers re-entering treated fields. Exposure durations are expected to be short- and intermediate-term.

In the current risk assessment, an oral Point of Departure (POD) is used for estimating risk via short- and intermediate-term inhalation exposure. The POD (no-observed adverse-effect level; NOAEL = 27 mg/kg/day) is based on a 28-day study in dogs. In the study, an increased incidence of mucosal edema in the gall bladder of both sexes was seen at the lowest-observed adverse-effect level (LOAEL) of 80 mg/kg/day.

Based on the oral NOAEL of 27 mg/kg/day, the lowest occupational handler inhalation MOE is 2,800 (mixing/loading of dry flowable formulations for groundboom application to sod farms). The lowest occupational handler inhalation MOE for the proposed seed treatments is 5,400 (mixing/loading liquids for commercial potato seed piece treatment). All residential handler

inhalation MOEs are ≥140,000, with the lowest MOE associated with mixing/loading/applying dry flowable formulations with a hand wand or backpack sprayer.

III. STUDY WAIVER REQUEST

A. Subchronic Inhalation Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: 1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more protective. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. ***Physical-Chemical Properties:*** Vapor pressure and Henry's law constant are key considerations with respect to volatilization after sprays have settled. Penthiopyrad has a low vapor pressure of 4.8×10^{-8} mm Hg at 25ºC. The Henry's law constant is 7.66×10^{-3} Pa m^3/mole at 20 ºC at pH 7. However, low vapor pressure and/or Henry's law constant do not preclude exposure to aerosolized droplets or particles/dust.

2. ***Use Pattern and Exposure Scenarios:*** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. HED acknowledges that airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift. In the case of penthiopyrad, mixing/loading dry flowable formulations using groundboom application to sod farms results in the highest inhalation exposure for occupational handlers.

3. ***Margins of Exposure (MOEs):*** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors

discussed here. Mixing/loading/applying using a handwand or backpack results in the highest residential inhalation exposure and an MOE of 140,000 for registered residential use sites. For occupational handlers, mixing/loading dry flowable formulations for application to sod farms using groundboom equipment resulted in the highest inhalation exposure and an MOE of 2,800 for registered use sites. The estimated inhalation MOEs for the proposed seed treatment uses are higher, with the lowest MOE of 5,400 for commercial seed treatment of potato seed pieces.

4. ***Toxicological Effects:*** Penthiopyrad shows low acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category III), and inhalation (Toxicity Category IV) routes of exposure and produces minimal eye irritation (Toxicity Category IV). No treatment-related findings were noted at necropsy in the acute inhalation study. It is not a dermal irritant or sensitizer.

   The liver and thyroid are target organs for penthiopyrad. Short-term oral exposure resulted in liver alterations (weight increases, enzyme changes, hypertrophy, and/or histopathology) in rats and mice at similar doses, and dogs at higher doses. Short-term exposure also resulted in thyroid changes in mice (hypertrophy) and rats (decreased weight, hypertrophy/proliferation, and hormone changes). Other effects observed were body weight changes and hematological alterations in rats and dogs, along with gallbladder effects (inflammation and edema) in dogs. A 28-day oral dog study was used to select the dose and endpoint for short- and intermediate-term inhalation exposure. The NOAEL of 27 mg/kg/day and LOAEL of 80 mg/kg/day were based on increased incidence of mucosal edema in the gall bladder of both sexes.

   No evidence of increased quantitative or qualitative susceptibility was observed in developmental toxicity studies on rats or rabbits or in a reproduction toxicity study on rats. However, increased quantitative susceptibility was seen in DNT studies in rats. Although increased quantitative susceptibility was observed, there is low concern for susceptibility, and there are no residual uncertainties regarding increased quantitative or qualitative pre- and/or postnatal susceptibility.

   Thyroid tumors in male rats and liver tumors in male mice were seen (carcinogenicity studies) after long-term exposure to penthiopyrad. The carcinogenic potential of penthiopyrad was reviewed by the Cancer Assessment Review Committee (CARC). Penthiopyrad was classified as having "Suggestive Evidence of Carcinogenicity," based on liver tumors in male mice.

   In considering a waiver request for an inhalation toxicity study, HED evaluates other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. More specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE depending on the exposure profile. According to HED's Integrated Structure, Toxicology, Endpoints and Properties (ISTEP) database, there were no other carboxamide pesticides with repeated dose inhalation toxicity studies. As such, there

were no available data showing that route-specific studies will be more protective for this class of compounds.

IV. HASPOC RECOMMENDATION

The HASPOC, based on a WOE approach, concludes that a subchronic inhalation toxicity study is not required for penthiopyrad at this time. This approach considered all of the available hazard and exposure information for penthiopyrad, including: (1) the low acute inhalation toxicity (Toxicity Category IV); 2) the physical/chemical properties of penthiopyrad including low volatility (4.8×10^{-8} mm Hg at 25ºC); and (3) the use of an oral POD results in MOEs ≥140,000 for residential exposures and MOEs ≥2,800 for occupational exposures.